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APPLICANT: Nigel Webb et al.

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FILING DATE: March 9, 1999

TITLE: FATTY ACID ANTI-CANCER CONJUGATES AND USES THEREOF

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CERTIFICATION OF FACSIMILE TRANSMISSION

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Typed or Printed Name of Person Signing Certification Edward R. Gates

Date: October 30, 2000

WG&S File Number: N0260/7031 (ERG)

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Attorney's Docket No. N0260/7031 (ERG)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Nigel L. Webb, et al.
Serial No.	:	09/265,307
Filing Date	:	March 9, 1999
For	:	FATTY ACID-ANTICANCER CONJUGATES AND USES THEREOF
Examiner	:	B. Trinh
Art Group	:	1612

CERTIFICATE OF FACSIMILE TRANSMISSION 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being facsimile transmitted to the United States Patent and Trademark Office in accordance with 37 C.F.R. §1.6(d) to the attention of Examiner Trinh, Washington, D.C. 20231, FAX number , 703-308-7922, on the 30th day of October, 2000.

Edward R. Gates

Commissioner for Patents
Washington, D.C. 20231

Sir:

RESPONSE

Applicant hereby responds to the Office Action dated July 21, 2000.

Applicant requests reconsideration of the final rejection in view of the following remarks.

It appears that the Examiner has withdrawn the art rejection which was based on a combination of references. Applicants gratefully acknowledge the withdrawal of this rejection. The exact language employed by the Examiner, however, appears to include some ambiguity. Applicants request the Examiner to acknowledge that the only rejection remaining is the one based on double patenting.

Regarding the double patenting rejection, applicants believe that the Examiner has not made outa *prima facie* case for rejecting the claims. The reasons for this are believed to be clear and fall into two categories, discussed below.

491422.1

The Examiner Has Not Made Out a Prima Facie Case Because the Examiner Has Not Identified The Differences Between the Pending Claims and The Bradley Patent and Has Not Discussed Why Those Differences Are not Patentably-Distinct Differences.

In any analysis of obviousness, it is the law that the differences between the pending claims and the prior art must be identified. The Examiner must then explain why those differences would have been obvious to one of ordinary skill in the art at the time of the invention. The Examiner has not done this, and, accordingly, has not met the requisite burden of making out a *prima facie* case for rejecting the claims.

For convenience, the Examiner has rejected all of the pending claims based on the following sentence:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant taxane embraces the taxol species and the fatty acid embraces the docosahexaeonic acid as a species.

The foregoing does not present a *prima facie* basis for rejecting the claims. The present claims are pharmaceutical composition claims, method of treatment claims, kit claims and pharmaceutical formulation claims. Each independent claim includes at least one limitation that is not present in the Bradley patent claims or obvious from the Bradley patent specification. The Examiner has not considered, identified or addressed such limitations, and, as such, has not made out a *prima facie* basis for rejecting the claims.

Just as an example, the method claims 17, 21 and 23 require administering a conjugate of a fatty acid and an anti-cancer agent, the conjugate being administered in an amount that is 10%, 50% and 100%, respectively, higher than the maximum tolerated dose of the unconjugated anticancer agent. These claims are based upon the unexpected finding that the conjugated form of the drugs surprisingly accumulates in cancer cells and less drug is available in other tissues, thereby reducing the dose-limiting toxicity of the anticancer compound. This was completely unexpected from the prior art, which, in fact, on the whole taught away from the higher doses employed in the present invention, as discussed in the prior amendment. (See, pages 2-5 of the April 2000 amendment.)

In the case of the conjugate DHA-paclitaxel, the maximum tolerated dose has been determined in a successful Phase-I clinical trial as being at least 1100 mg/m^2. This is more than four times the accepted maximum tolerated dose of paclitaxel alone, which is 225 mg/m^2. Thus, as described and claimed, more than 10%, 50% and 100% of paclitaxel's maximum tolerated dose has been administered as a conjugate.

This is nowhere discussed or suggested even remotely in the prior art. To the contrary, the prior art suggested administering amounts that are the same as or even less than the amounts typically used for administering the unconjugated anticancer compounds.

Similar discussion can be made with respect to other patentably-distinct limitations set forth in the other independent claims. These limitations are discussed at page 3 of the prior amendment and are summarized again at page 5 of the prior amendment. As mentioned above, the Examiner has not considered or addressed these specific claim limitations in rejecting the claims, and, therefore, the Examiner has not made out a *prima facie* case for rejecting these claims on the basis of double patenting.

The Examiner Also Has Not Made Out a *Prima Facie* Case Because the Examiner Has Not Addressed The Unexpected Results Detailed in the Specification and in the April Amendment and Relied Upon For Patentability.

An Examiner cannot ignore unexpected results alleged and demonstrated. These unexpected results are over and above the teachings of the cited Bradley patent. The present application was filed based upon the surprising results obtained using a conjugate of the Bradley patent, and the Examiner has not provided any basis to question the applicants' statements about such unexpected results. Absent such, the Examiner has not met his burden in rejecting the claims and no longer has a *prima facie* basis for rejecting the claims. The unexpected results are detailed at page 3 of the prior amendment. The law relating to unexpected results is also detailed in the prior amendment.

The applicants note that the assignee of the present invention, Protarga, Inc., now has completed its Phase I clinical trial, supervised by clinicians at Johns Hopkins, one of the most prestigious cancer institutes in the world. The results of that trial were the identification of the dose which is to be given in the Phase II evaluation, 1100 mg/m^2. This dose is more than four times the amount of paclitaxel previously approved for unconjugated paclitaxel. In addition, patients receiving these higher amounts had fewer side effects than with unconjugated paclitaxel. These results were presented at the "2000 International Symposium on Tumor-Targeted Delivery Systems" held in Bethesda, Maryland in September of 2000. These results also were presented at CapCure, in September of 2000 and at the Gordon Research Conference entitled "Chemotherapy of Experimental Clinical Cancer" held at Oxford University, UK, in September, 2000. A copy of the September 2000 presentations is enclosed herewith. Applicants could submit a declaration to this effect, if it would be persuasive to the Examiner.

It is believed that the present claims are patentably distinct from the Bradley patent and that the Examiner has no present basis for rejecting the claims.

Applicants note the previous request for an opportunity to interview this case should the Examiner not be persuaded by applicants' response. Applicants also requested an opportunity to reintroduce into this case dependent claims which were canceled upon the filing of this application, should an independent claim be allowed.

The Examiner is encouraged to contact the undersigned attorney by telephone to advance the prosecution of this application.

Respectfully submitted,

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Attorney Docket No: N0260/7031 (ERG)
October 30, 2000
X 11/21/00

Tumor Targeting by Conjugation of a N

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[1]Protarga, Inc., 1100 East Hector Street – Suite 450, Conshohocken, PA 19428 [2]The Johr

Abstract

Targeting an anti-cancer drug to tumors should increase the Area Under the drug concentration—time Curve (AUC) of the drug in tumors while decreasing the AUC in normal cells, and should therefore increase the therapeutic index of that drug. Anti-tumor drugs typically have half-lives far shorter than the cell cycle transit times of most tumor cells. Tumor targeting will increase the proportion of cells that move into cycle when the drug concentration is high, which should result in more tumor cell killing. In an effort to test that hypothesis, we conjugated a natural fatty acid, docosahexaenoic acid (DHA), to paclitaxel through an ester bond to the paclitaxel 2'-oxygen. The resulting paclitaxel fatty acid conjugate, DHA-paclitaxel, does not assemble microtubules and is therefore non-toxic. In the M109 mouse tumor model, DHA-paclitaxel is less toxic than paclitaxel, but causes complete regressions in 10/10 animals, whereas paclitaxel causes 0/10 complete regressions.

One explanation for the greater therapeutic index of DHA-paclitaxel relative to paclitaxel is that the fatty acid alters the pharmacokinetics to increase the tumor AUC while decreasing the AUC in normal cells. To test that possibility, we compared the pharmacokinetics of DHA-paclitaxel with paclitaxel in CD2F1 mice bearing ~ 125 mg sc M109 tumors. The mice were injected at zero time with a bolus of either DHA-paclitaxel or paclitaxel formulated in 10% Cremophor®/10% ethanol/80% saline. Animals were sacrificed as a function of time out to 14 days. Tumors and plasma were frozen and stored. The concentrations of paclitaxel and DHA-paclitaxel were analyzed by LC/MS/MS. The results show that the conjugation of paclitaxel to DHA targets paclitaxel to tumors while limiting paclitaxel AUC in plasma. The tumor AUC is 61-fold higher for DHA-paclitaxel than for paclitaxel at equitoxic doses and 8-fold higher at equimolar doses. Likewise, at equitoxic doses, the tumor AUC of paclitaxel derived from Lv. DHA-paclitaxel is 6.1-fold higher than for paclitaxel derived from Lv. paclitaxel. The tumor concentration of paclitaxel following Lv. paclitaxel drops rapidly, so that by 16 hrs it has fallen to the same concentration (2.8 μM) produced one week following an equitoxic dose of DHA-paclitaxel. In plasma, paclitaxel AUC following an MTD dose of DHA-paclitaxel is approximately 0.5% of DHA-paclitaxel AUC, and is only 1.8 times the plasma AUC of paclitaxel following an equitoxic dose of paclitaxel. Thus the increase in tumor AUC and the limited plasma AUC of paclitaxel following DHA-paclitaxel administration are consistent with the increase in therapeutic index observed for DHA-paclitaxel relative to paclitaxel in the M109 mouse tumor model.

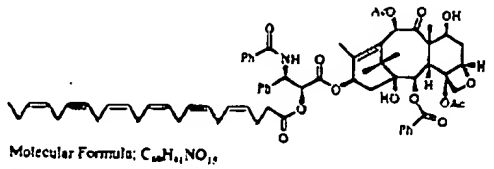
A Phase I clinical study is underway at The Johns Hopkins Hospital to evaluate the safety of DHA-paclitaxel in patients with a variety of solid tumors. Twenty-one patients have been treated to date, including 3 patients with prostate cancer. The recommended Phase II dose has been set at 1100 mg/m², which is equivalent to 4.6 times the maximum approved paclitaxel dose on a molar basis. No alopecia or significant peripheral neuropathy, nausea, or vomiting have been observed. Asymptomatic, transient neutropenia has been the primary side effect. Ten of 19 patients, including 1 of 3 prostate patients, transitioned from progressive to stable disease, as assessed by follow-up CT. Significant quality of life improvements have been observed.

Thus, DHA-paclitaxel is well tolerated in patients and cures tumors in mice by targeting drug to tumors.

Introduction

- The preferential localization, or targeting, of a cytotoxic drug to a tumor, while simultaneously reducing exposure and cytotoxicity to normal cells, should increase the therapeutic index of such a drug and lead to better cancer chemotherapy.
- The natural fatty acid docosahexaenoic acid (DHA) was conjugated to paclitaxel at the 2'-oxygen in order to meet the following objectives:
  - inactivate the cytotoxicity of the resulting paclitaxel fatty acid conjugate (DHA-paclitaxel), thus reducing toxicity to normal tissue.
  - target drug to tumors to increase therapeutic index relative to paclitaxel.
- The results indicate that DHA-paclitaxel possesses a greater therapeutic index in tumor-bearing mice relative to paclitaxel, because the conjugate is targeted to tumors and is non-toxic until converted to paclitaxel within tumors.

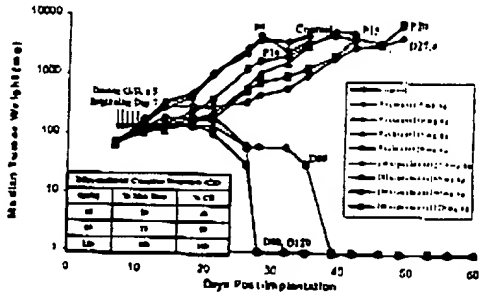
1. DHA-paclitaxel:
The active ingredient in *Taxoprexin®* Injection



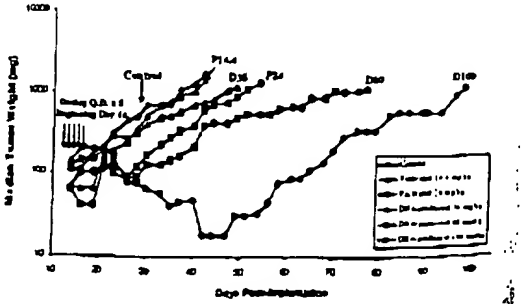
Molecular Formula: $C_{68}H_{81}NO_{15}$

Component	Molecular Weight	% of DHA-paclitaxel
DHA	328	27%
Paclitaxel	853	73%
DHA-paclitaxel	1164	100%

2. DHA-paclitaxel is More Active than Paclitaxel in the Mouse M109 Lung Carcinoma Model



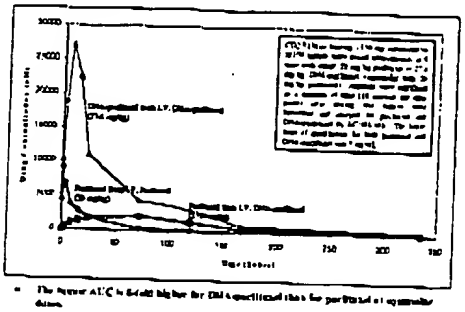
3. DHA-paclitaxel is More Active than Paclitaxel in the HT-29 Human Colon Carcinoma Model (Data from SKB)



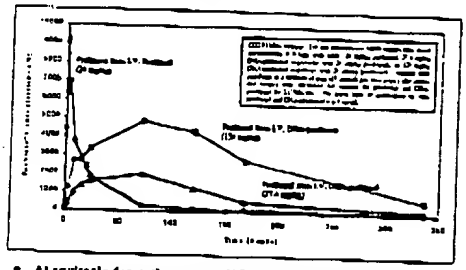
ıtural Fatty Acid to Paclitaxel

ın,[1] Prabu Devanesan,[1] Nigel L. Webb,[1] Glenn J. Fegley,[1] Sharyn D. Baker,[2] Antonio
opkins Oncology Center, Cancer Research Building, 1650 Orleans Street, Baltimore, MD 21231

4. M109 Tumor Concentrations of DHA-paclitaxel and Paclitaxel Following Single I.V. Doses of DHA-paclitaxel or Paclitaxel



5. M109 Tumor Concentrations of Paclitaxel Following Single I.V. Doses of DHA-paclitaxel or Paclitaxel

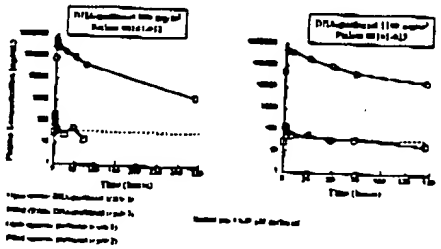


- At equitoxic doses, the tumor AUC of paclitaxel derived from i.v. DHA-paclitaxel is 6-fold higher than for paclitaxel derived from i.v. paclitaxel.

6. AUCs in Mouse Plasma and M109 Tumors for i.v. Paclitaxel, i.v. DHA-paclitaxel, and Paclitaxel Derived from i.v. DHA-paclitaxel

Drug	Dose (mg/kg)	Plasma AUC (μM x hour) Pac	Plasma AUC (μM x hour) DHA-pac	Tumor AUC (μM x hour) Pac	Tumor AUC (μM x hour) DHA-pac
Pac	20	33.4	—	155	—
DHA-pac	27.4	25.5	2,218	286	1,242
DHA-pac	120	56.9	12,576	939	9,437

7. DHA-paclitaxel and Paclitaxel Plasma Concentrations Following i.v. Administration of *Taxoprexin*® DHA-paclitaxel to Humans



8. DHA-paclitaxel Pharmacokinetic Parameters in Phase I Patients

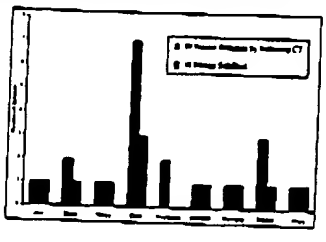
Dose (mg/m²)	$t_{1/2}$ (hr)	V_d (L)	Cl (L/hr)
820	21	3.7	0.14
1100	24	3.9	0.12

Abbreviations: terminal half-life ($t_{1/2}$), volume of distribution at steady state (V_d), systemic clearance (Cl).

9. Conclusions from *Taxoprexin*® DHA-paclitaxel Pharmacokinetic Studies in Humans

- DHA-paclitaxel remains intact and inert in plasma:
  < 0.05% of DHA-paclitaxel is converted to cytotoxic paclitaxel in plasma
- Compared to paclitaxel, DHA-paclitaxel has
  - a 40X smaller volume of distribution (3.9 L), indicating less extravascular distribution and/or less tissue binding for DHA-paclitaxel (may explain fewer side effects vs. paclitaxel)
  - a 200X lower clearance rate (~0.12 L/hr) (rare even in blood)
- DHA-paclitaxel exposure increases with increasing doses of DHA-paclitaxel (clinical dose adjustments are feasible)
- Interpatient variability in DHA-paclitaxel exposure is ~2-3-fold (acceptable)

10. Phase I: Patients Evaluated and Stabilized



C. Wolff,[2] and Ross C. Donehower[2]

11. Main Conclusions of *Taxoprexin*® Phase I Study Results

First reported by Johns Hopkins at the May 2000 meeting of the American Society of Clinical Oncology

- DHA-paclitaxel is very well tolerated as a 2h infusion every 21 days. More frequent dosing may not be necessary.
- 21 patients treated at The Johns Hopkins Hospital
- 1100 mg/m² will be the Phase II dose (which provides 4.6 times the taxane drug provided by the maximum approved dose of paclitaxel, on a molar basis)
- No hair loss or neuropathy, in contrast to *Taxol*® and *Taxotere*®
  - Possibly related to lower PAC C_{max} following DHA-PAC infusion.
- No nausea or vomiting
- Asymptomatic, transient neutropenia is the primary side effect
- 10 of 19 patients transitioned from progressive to stable disease as assessed by follow-up CT
- Quality of life improvement

Conclusions

- DHA-paclitaxel is less toxic than paclitaxel because DHA-paclitaxel is not significantly converted to paclitaxel in plasma.
- The tumor AUC of DHA-paclitaxel is increased 61-fold relative to the tumor AUC of paclitaxel at equitoxic doses, and 8-fold at equimolar doses. Therefore, DHA targets drug to tumors.
- The tumor AUC of paclitaxel derived from DHA-paclitaxel is increased 6-fold relative to the tumor AUC of paclitaxel following an equitoxic dose of paclitaxel.
- These observations are consistent with the increase in therapeutic index observed for DHA-paclitaxel relative to paclitaxel in the M109 mouse tumor model.
- In a Phase I clinical study, DHA-paclitaxel has produced no alopecia or significant peripheral neuropathy, nausea, or vomiting. Neutropenia is the dose-limiting toxicity in both humans and animals.
- The recommended Phase II dose has been set at 1100 mg/m², which provides 4.6 times the taxane drug provided by the maximum approved dose of paclitaxel, on a molar basis.

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